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ORIGINAL ARTICLE

Scaling and root planing with enhanced root planing on healthcare for type 2 diabetes mellitus: A randomized controlled clinical trial



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Abstract *Background/purpose:* Periodontitis is related to diabetes mellitus. However, whether periodontal therapy can affect glycemic control remains unclear. This study aims to evaluate the effects of scaling and root planing (SRP) as well as enhanced root planing (ERP) on the glycemic control and periodontal condition of patients with type 2 diabetes mellitus (T2DM) and chronic periodontitis.

Materials and methods: Patients with T2DM and chronic periodontitis were randomly assigned to treatment ($n = 49$) and control ($n = 22$) groups. The treatment group was treated with SRP, whereas the control group remained untreated. After 3 months, the patients in the treatment group were randomly divided into sub-ERP ($n = 25$) and subprophylaxis ($n = 24$) groups, which were treated with ERP and prophylaxis, respectively.

Results: Hemoglobin A1c and fast plasma glucose levels in the treatment group decreased after SRP treatment. The changes in the hemoglobin A1c level in this group was significantly greater than that in the control group ($P < 0.05$). The periodontal condition significantly improved in the treatment group compared with that in the control group ($P < 0.01$). The decrease in periodontal pocket depth in the sub-ERP group was more significant than that in

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the subprophylaxis group ($P < 0.05$).

Conclusion: This study suggests that SRP can be of benefit for the improvement of glycemic control and periodontal condition. In addition, ERP can further improve the periodontal condition of patients with T2DM.

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Introduction

Glycemic control is a perennially important issue for people with diabetes mellitus. A number of acute (hyperglycemic hyperosmolar state, hypoglycemia, and ketoacidosis) and chronic (cardiovascular disease, nephropathy, retinopathy, neuropathy, etc.) complications are caused by prolonged hyperglycemia; some of the complications may even lead to death.¹ The United Kingdom Prospective Diabetes Study in the United States demonstrated that well-controlled hyperglycemia in type 2 diabetes mellitus (T2DM) can reduce the risk of long-term diabetes mellitus complications.²

Periodontitis, a common public health issue, has been considered a complication of T2DM.^{3,4} It is an inflammatory disease that leads to periodontal tissue destruction.⁵ Periodontal tissue destruction is mediated by bacterial toxins and inflammatory cytokines in response to bacterial flora and their products.⁶ The total surface area of the inflamed and ulcerated epithelium of the periodontal pocket in an individual with periodontitis is at least equal to the surface area of the palm of the hand.⁷ The bacteria and their toxin may enter the blood from this ulcerated area and lead to systemic inflammation, which plays a major role in insulin sensitivity and glucose dynamics.

As part of nonsurgical periodontal therapy, scaling and root planing (SRP) is the major and most important treatment method for periodontitis. This technique includes supragingival/subgingival SRP. A number of studies investigated the effect of nonsurgical periodontal treatment on patients with T2DM. Several research groups reported that improvements in the periodontal condition can promote glycemic control.^{8–13} In a previous study, O'Connell et al¹⁰ designed a 30-sample trial to treat T2DM patients with SRP + doxycycline or SRP + placebo, which yielded 1.5% (SRP + doxycycline) and 0.9% (SRP + placebo) reduction in the HbA1c level. Rodrigues et al⁸ performed trials similar to that conducted by O'Connell et al; however, they found that HbA1c significantly improved only in the SRP alone group. Grossi et al¹³ also observed improvements in HbA1c after SRP administration with doxycycline. Yun et al¹² arranged two groups that were treated with systemic administration only or SRP plus doxycycline, respectively. The results show that both groups exhibited a reduction in the HbA1c level; however, no significant difference between the two groups was observed. Navarro-Sanchez et al⁹ and Faria-Almeida et al¹¹ compared the effects of SRP on T2DM and nondiabetic patients, and found that HbA1c significantly decreased in the T2DM group. These studies were not randomized controlled trials (or the HbA1c outcomes were not analyzed between treatment and control groups). In addition, the results of parts of the studies were combined with the systemic administration of antibiotics.

Several studies reported the HbA1c reduction trends but without indicating any statistical significance. Stewart et al¹⁴ designed a clinical study on 72 T2DM patients with periodontitis and suggested that periodontal therapy may be associated with improvements in glycemic control. However, the results had insufficient statistical value. Jones et al¹⁵ reported a randomized trial on 165 veterans with poorly controlled diabetes over 4 months. They noted that periodontal therapy showed promise in improving the glycemic control without statistical significance. Another study reported that periodontal therapy showed no significant effect on the medical diabetes data through a clinical study that involved seven insulin-dependent diabetics and 13 noninsulin-dependent diabetics.¹⁶ Given the incompatible results that can be created by the different study conditions, such as different inclusion and exclusion criteria as well as distinct interventions, this single-blind randomized controlled study aims to determine the relationship between SRP and glycemic control under relatively strict clinical and experimental conditions in a Chinese population with a low-calorie diet.

Although some authors reported that repeated SRP has no additional effect on periodontal pocket reduction and attachment gain compared with a single initial instrumentation,¹⁷ repeated root planing can reduce the number and proportions of periodontopathogenic bacteria in subgingival plaque.¹⁸ Sigusch et al¹⁹ described a treatment concept called second enhanced root planing (ERP), which is an additional therapy to the initial SRP, and proved that ERP can yield better long-term treatment outcomes on aggressive periodontitis. Whether ERP could bring better prognosis to chronic periodontitis accomplished with T2DM similar to aggressive periodontitis should be determined. Moreover, an increased postoperative infection on diabetes after surgery was observed. King et al²⁰ reported the possibility of increased postoperative infection when the mean 24-hour postoperative glucose concentration exceeds 150 mg/dL (8.3 mmol/L) after noncardiac surgery. Thus, clinicians are always in a dilemma to determine whether to continue with surgery or maintained phase (prophylaxis scaling is the typical procedure that removes plaque and calculus deposit) after initial periodontal treatment. Therefore, this study also determined whether ERP can yield higher curative effect on periodontitis with T2DM.

Materials and methods

Sample population

Recruitment of participants for this single-blind, randomized, controlled clinical trial was started in July 2010. The

entire trial was completed in May 2011. A total of 400 T2DM patients from the Hubei Provincial Government Hospital (Wuhan, Hubei, China) were examined. Of these patients, 75 were recruited according to the inclusion criteria, and informed consents were obtained. A questionnaire was used to obtain the general information of patients, including gender, date of birth, smoking habits, alcohol consumption, present glycemic control scheme, and date of DM diagnosis. The clinical trial was approved by the ethics committee (School and Hospital of Stomatology, Wuhan University) with approval number 200712. The clinic registration number is ChiCTR-CCC-00000365.

All individuals who participated in this study had chronic periodontitis and had been diagnosed to have T2DM for more than 1 year. A diagnosis of T2DM should meet at least one of the following criteria: (1) postprandial plasma glucose ≥ 200 mg/dL (11.1 mmol/L); (2) fast plasma glucose (FPG) ≥ 126 mg/dL (7.0 mmol/L); (3) 2-hour oral glucose tolerance test ≥ 200 mg/dL (11.1 mmol/L). In addition, patients should have the following attributes: (1) 35 to 80 years old; (2) with at least 16 natural teeth; (3) with at least four teeth with probing pocket depth (PPD) ≥ 5 mm, clinical attachment loss (CAL) ≥ 4 mm, and bleeding on probing (BOP), distributed in two or more oral quadrants; and (4) the HbA1c level within 3 months before recruitment should at least be 5.5%. The following exclusion criteria were adopted: (1) accompanied with other systemic immune diseases; (2) administered with antibiotics, immunomodulators, contraceptives, or any other form of hormone within the past 3 months; (3) underwent modified diabetes treatment strategy within 3 months; (4) had periodontal treatment within the past 12 months; (5) needed extraction or endodontic treatment; (6) smokes more than four cigarettes per day; (6) pregnant or lactating women. Patients were dropped from the study if these conditions were met during the study course: (1) the diabetes treatment scheme was changed; (2) drugs were systemically administered; (3) the patients could not revisit on time; and (4) the participants were lost on follow-up.

Sample size calculation

A preliminary trial was conducted on 10 patients with periodontitis and T2DM. Five patients received SRP, whereas the remaining patients were untreated. The change in the HbA1c level from the baseline value to 3 months after therapy was recorded. The sample size was calculated using the PASS software (version 11; NCSS, Kaysville, Utah, USA). The magnitude of the change in HbA1c was 0.20%. Given the 80% statistical power, 20 patients in the control group and 40 patients in the treatment group were required with $\alpha = 0.05$.

Study design and procedure

The recruited patients were instructed to maintain their previous diet and exercise habits and to inform the authors whenever their glucose control treatment was changed. After baseline evaluation, patients were randomly assigned into two groups at a sample ratio of 2:1. Thus, 50 and 25 patients were included in the treatment and control groups,

respectively. Patients in the treatment group underwent oral health instructions, supra-/subgingival scaling (Cavitron Bobcat Pro, Dentsply, York, PA, USA), and manual curettage (Hu-Friedy, Chicago, IL, USA), which were completed within 2 weeks after the baseline evaluation. They were then recalled for evaluation of their periodontal and biochemical parameters (Evaluation2) 3 months after treatment. Afterward, the patients in the treatment group were randomly divided into the sub-ERP and subprophylaxis groups. Patients in the sub-ERP group again received full-month ultrasonic scaling and manual root planing of the teeth with PPD ≥ 4 mm. Meanwhile, the subprophylaxis group received only full-month ultrasonic scaling to remove calculus and plaque. Three months after the second intervention, all parameters were measured for the third time (Evaluation3). The control group was not given any periodontal treatment except for evaluations at the baseline as well as on the 3rd and 6th months. The procedure used in this study is described in Fig. 1. After completion of the entire study, all volunteers in the control group received initial periodontal treatment in accordance with the provisions of the informed consent form. Assignment to different groups was made using pre-prepared randomization in group A, B, or C. Participants with A and B were assigned to the treatment group and then respectively assigned to the sub-ERP and subprophylaxis groups, whereas individuals with C were assigned to the control group. Cards with group identification were prepared and placed in number-coded envelopes as defined by SPSS (version 17.0; IBM, New York, NY, USA). The random code was retained until the last patient had completed the entire study. The single blind method was used in this study as the examiner was blind to the intervention for the patients.

Outcome measures

The primary outcome measure was the HbA1c level evaluated thrice in treatment and control groups. The secondary outcomes were the FPG level and periodontal parameters, which were also evaluated. The changes in the periodontal condition after ERP or prophylaxis were also determined.

All patients were subjected to a periodontal clinical examination, which was performed in six sites per tooth (excluding the third molar) by a trained calibrated examiner. The plaque index,²¹ BOP, PPD, and distance from the gingival margin to the cemento–enamel junction were examined using a Williams periodontal probe. If the gingival margin is located apically to the cemento–enamel junction, the distance from the gingival margin to the cemento–enamel junction is recorded positively. Thus, the clinical CAL can be calculated by adding PPD to this distance. The FPG and HbA1c levels were measured using an automatic biochemical analyzer (Beckman DXC800, USA) and an HbA1c analyzer (Drew Scientific D55, England, UK) in the Clinic Laboratory Department of Wuhan General Hospital of Guangzhou Military (Wuhan, Hubei, China). All parameters were examined within 3 days before or later than the predetermined time.

Examiner calibration

The whole-mouth CAL was recorded by a single examiner in three chronic periodontitis patients, and this was repeated

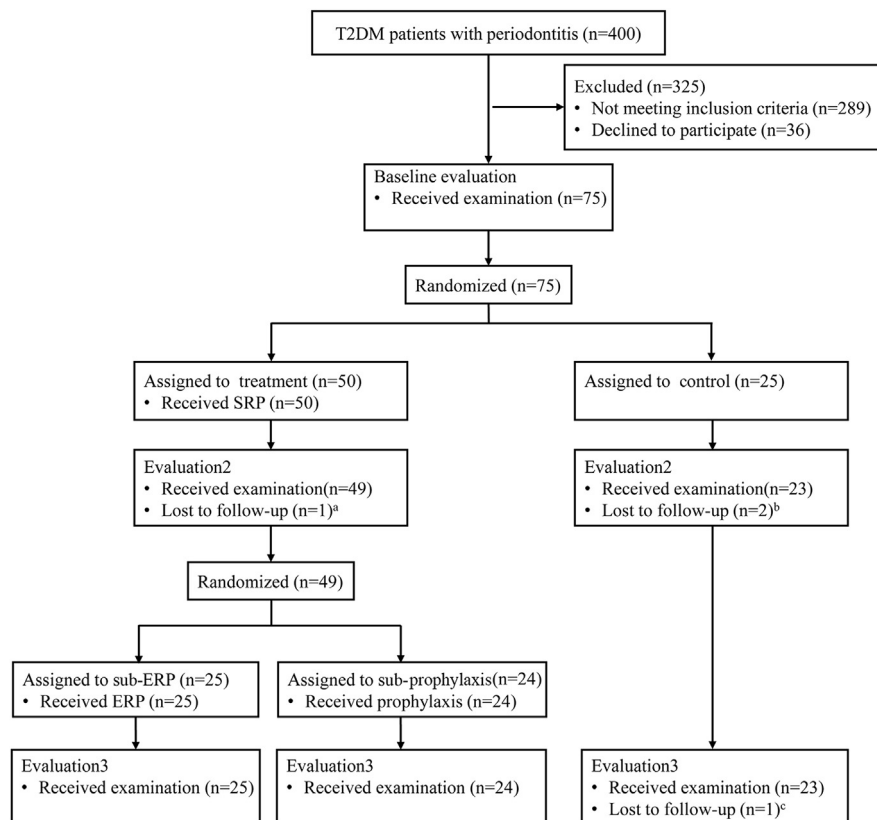


Figure 1 Flow diagram of this study. (a) One patient was lost to follow-up because of a business trip. (b) One patient quit because he could not revisit on time and another quit voluntarily. (c) One patient quit voluntarily.

24 hours later. Then, the intraexaminer reproducibility for CAL was measured, and K coefficient (± 1 mm) = 0.87.

Statistical analysis

Data were analyzed using SPSS (17.0). For BOP, the percentage of positive sites was obtained for each patient before the mean \pm standard deviation of each group was calculated. The mean and standard deviation of plaque index, PPD CAL, FPG, and HbA1c for each group were also calculated.

The baseline balance between groups was determined using the independent-sample t -test or the Pearson χ^2 test. In each group, the differences between three evaluations were analyzed using the paired-sample t -test. The differences after the interventions between groups were analyzed using the independent-sample t -test. Statistical significance was determined at an α level of 0.05.

Although not part of the original protocol, the patients in the treatment group were reclassified as follows: patients who exhibited reduced or unchanged/increased HbA1c levels 3 and 6 months after treatment were classified as effective or ineffective, respectively. The median and interquartile range of the baseline FPG and HbA1c levels in the two groups were calculated and analyzed using the Mann–Whitney U -test to determine the relationship between the baseline glycemic condition and the effect of SRP on HbA1c.

Results

Sample statistics

A total of 71 of the 75 recruited patients finished the study. One patient in the treatment group was lost to follow-up because he went on a business trip. Two patients in the control group quit voluntarily, whereas another quit because he could not revisit on time (Fig. 1). The missing data of the patients who quit were checked. The results show that the missing data are not related to the outcomes. Thus, the missing patients were ignored in the analysis because they were missing at random completely.

No relevant differences in the general data (age, gender, DM duration, smoking, alcohol consumption, drugs prescription, other systemic diseases, and family history of DM) were found. In addition, no significant differences between the baseline periodontal and glycemic parameters of the treatment and control groups were observed (Table 1).

Primary outcome

The HbA1c level in the treatment group decreased from Baseline to Evaluation2 ($7.68 \pm 1.22\%$ vs. $7.54 \pm 1.13\%$, $P < 0.01$) and to Evaluation 3 ($7.68 \pm 1.22\%$ vs. $7.51 \pm 1.31\%$, $P < 0.05$). Compared with the control group, the change in the HbA1c level from Baseline to Evaluation2

Table 1 Characteristics of sample populations at baseline.

Characteristic	Treatment group (n = 49)	Control group (n = 22)	P
Age (y)	60.4 ± 9.77	62.7 ± 10.7	0.377
Gender (male/female)	21/28	10/12	0.838
Duration of DM (y)	8.63 ± 4.20	7.29 ± 5.61	0.305
Hypoglycemic drug			
Oral drug	40	15	0.210
Insulin	30	11	0.376
Family history of DM	13	8	0.401
Other systemic diseases			
Hypertension	20	10	0.714
Hyperlipemia	17	9	0.615
Cardiocerebral vascular diseases	15	6	0.776
Smoking	12	6	0.803
Alcohol consumption	13	7	0.647
Periodontal indices			
PI	1.78 ± 0.60	1.73 ± 0.49	0.724
BOP (%)	55.7 ± 16.5	52.8 ± 15.0	0.480
PPD (mm)	2.50 ± 0.45	2.43 ± 0.47	0.593
CAL (mm)	3.41 ± 0.97	3.33 ± 0.97	0.752
Glycemic parameters			
FPG (mmol/L)	7.68 ± 0.90	7.51 ± 1.13	0.486
HbA1c (%)	7.68 ± 1.22	7.38 ± 1.30	0.360

Data set represented as mean ± SD or numbers of samples. BOP = bleeding on probing; CAL = clinical attachment loss; DM = diabetes mellitus; FPG = fasting plasma glucose; HbA1c = hemoglobin A1c; PI = plaque index; PPD = probing pocket depth.

in the treatment group exhibited statistical difference ($0.13 \pm 0.34\%$ vs. $-0.03 \pm 0.22\%$, $P < 0.05$) (Fig. 2B).

Secondary outcome

In the treatment group, the FPG level decreased from Baseline to Evaluation2 (138 ± 16 vs. 135 ± 20 mg/dL, $P < 0.05$) and to Evaluation3 (138 ± 16 vs. 135 ± 19 mg/dL, $P < 0.05$). Compared with the control group, no statistical difference was found in the change in FPG ($P > 0.05$) (Fig. 2A).

All clinical periodontal parameters in the treatment group significantly improved from Baseline to Evaluation2

and to Evaluation3 compared with those in the control group ($P < 0.01$) (Fig. 3). A statistical difference was found only in the change in the PPD level from Evaluation2 to Evaluation3 between the sub-ERP and subprophylaxis groups (-0.03 ± 0.13 vs. 0.03 ± 0.08 , $P < 0.05$) (Fig. 4).

Baseline glycemic condition after reclassification in terms of SRP effect

After being classified as Effective and Ineffective according to the HbA1c level variations observed 3 months after the first intervention, the patients showed significant higher baseline FPG levels (median, 7.84; interquartile range,

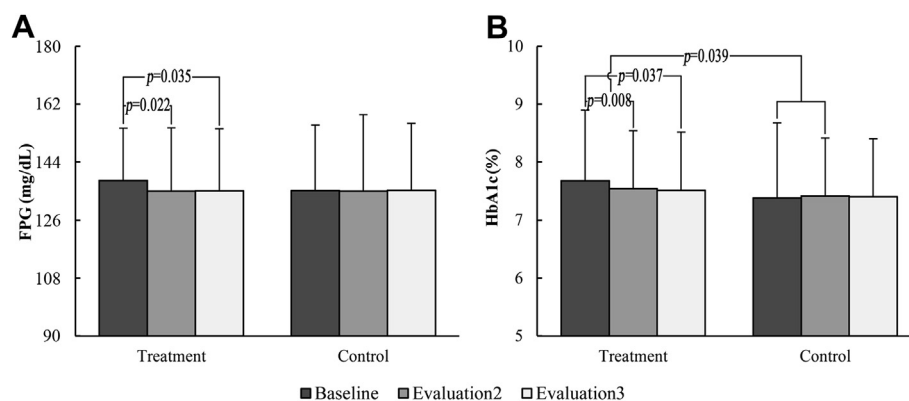


Figure 2 Glycemic parameters of the treatment and the control groups during Baseline evaluation, Evaluation2, and Evaluation3. All values are presented as mean ± SD. Inner-group differences were analyzed using paired-sample *t*-test, and intergroup differences were determined using independent-sample *t*-test.

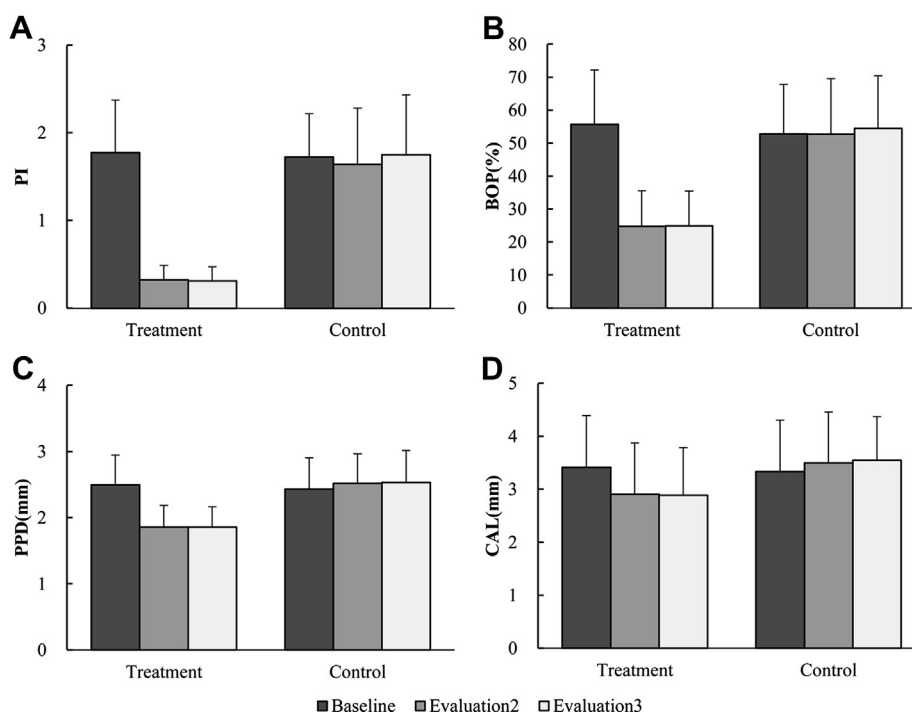


Figure 3 Clinical periodontal indices in the treatment and control groups during Baseline evaluation, Evaluation2, and Evaluation3. All values are presented as mean \pm SD. Statistical significance is not shown in the figure. Inner-group differences were analyzed using paired-sample *t*-test, and intergroup differences were determined using independent-sample *t*-test.

7.30–8.71) in the Effective class compared with those in the Ineffective class (median, 7.40; interquartile range, 6.76–8.12; $P < 0.05$) (Fig. 5A). The baseline HbA1c level in

the Effective class was also higher (median, 7.80; interquartile range, 7.00–8.70) than that in the Ineffective class (median, 7.30; interquartile range, 6.52–7.95; $P > 0.05$),

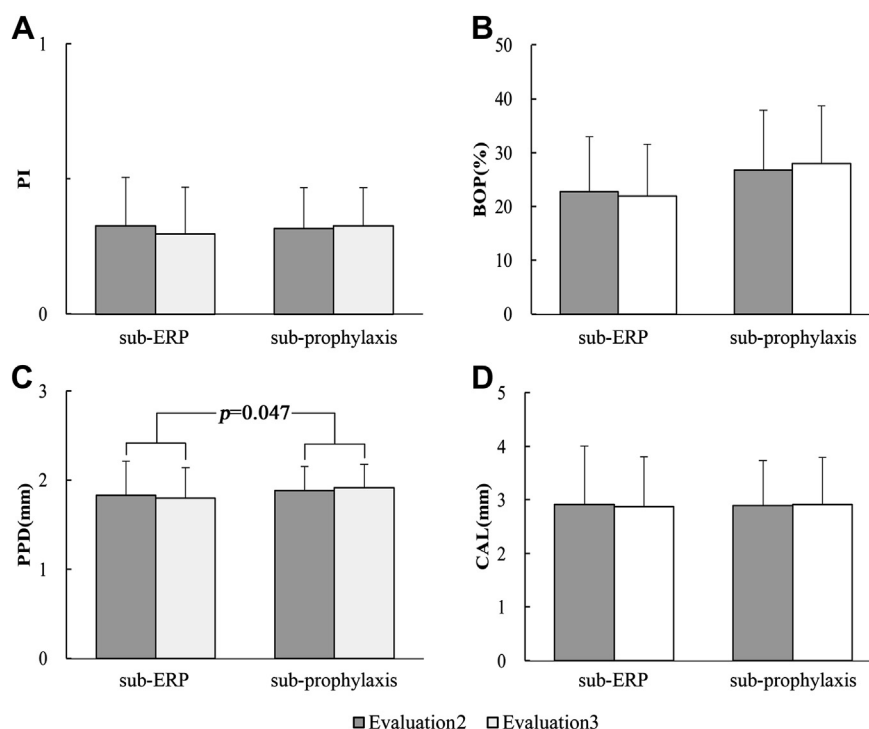


Figure 4 Periodontal indices in the sub-ERP (enhanced root planing) and subprophylaxis groups during Evaluation2 and Evaluation3. All values are presented as mean \pm SD. Inner-group differences were analyzed using paired-sample *t*-test, and intergroup differences were determined using independent-sample *t*-test.

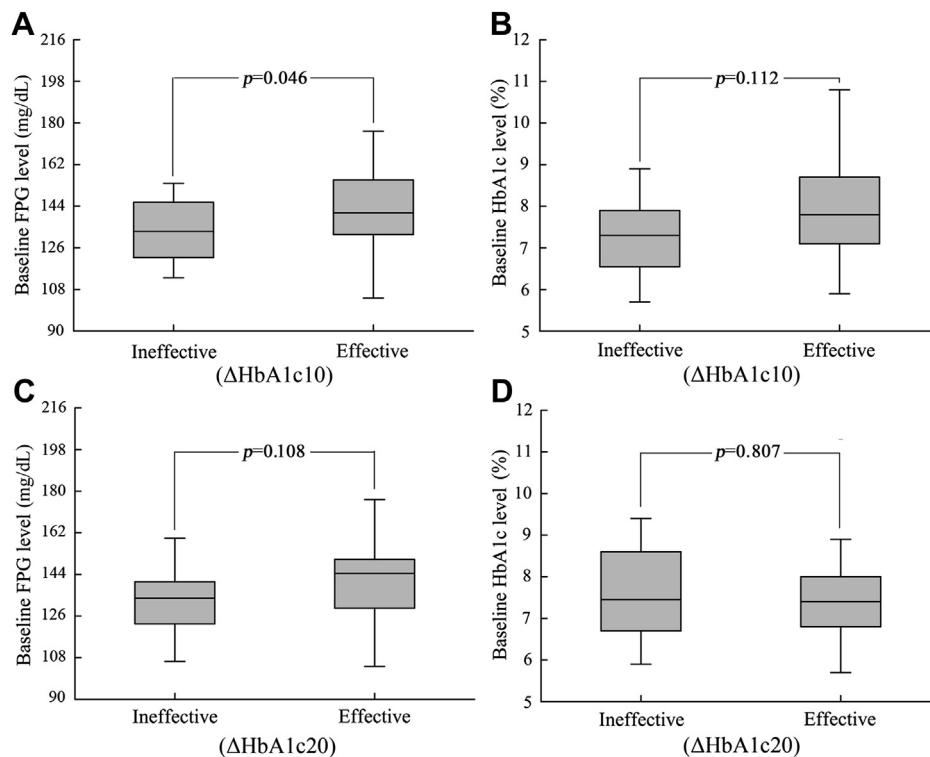


Figure 5 Baseline glycemic parameters of patients categorized in terms of changes in the HbA1c levels. The box plot shows the median, interquartile range, and min/max values. (A, B) Patients categorized with first scaling and root planing (SRP) effect. (C, D) Patients categorized with first SRP effect. Effective: patients with reduced hemoglobin A1c (HbA1c) levels. Ineffective: patients with increased or unchanged HbA1c levels. The differences between groups were analyzed using the nonparametric Mann–Whitney *U* test.

but did not reach statistical significance (Fig. 5B). When classified according to the results obtained on the 6th month, no clear difference in the baseline FPG and HbA1c levels was found (Fig. 5C and D).

Discussion

Whether SRP can improve diabetes mellitus remains controversial. HbA1c is one of the most important markers in T2DM patients and is used to evaluate the severity of diabetes as well as the glucose control condition. Any reduction in the HbA1c level is likely to reduce the risk of complications. Each 1% reduction in the HbA1c level would bring a relative risk reduction of 21% for any diabetes-related endpoint, 21% for diabetes-related deaths, 14% for myocardial infarction, and 37% for microvascular complications.²² In this study, the HbA1c level in the treatment group showed 0.17% ($0.17 \pm 0.08\%$, $P = 0.039$) reduction during the evaluation at 3 months and 0.18% ($0.18 \pm 0.12\%$, $P = 0.121$) reduction at 3 and 6 months after treatment, respectively, compared with those in the control group (Fig. 2B). This finding suggests that SRP can reduce the plasma glucose level of T2DM patients. Simpson et al²³ performed a meta review and reported that the mean percentage difference in HbA1c after scaling/root planing and oral hygiene (\pm antibiotic therapy) versus no treatment/usual treatment after 3–4 months was -0.40% , a value higher than that obtained in the present study. As

part of the included studies characterized by an accompanying antibiotic administration,^{12,15} the results may not only reflect the SRP effect alone. Notably, tetracycline and its derivatives can directly act on insulin production; thus, the reduction in the HbA1c level may be attributed to antibiotic administration.²⁴ These conditions suggest that SRP helps improve glucose control. By contrast, the FPG level is an inferior screening parameter because of the high variability of the experimental conditions, such as the carbohydrate content of the last meal as well as the energy expenditure between the last meal and the measurement. Consequently, FPG has been used in combination with HbA1c in many interventional trials that involve either dietary measures or hypoglycemic drugs to evaluate the glycemic control condition.^{25,26} Fig. 2 shows a significant reduction in the FPG level of the treatment group after SRP, thus confirming the SRP effect on glycemic control.

As previously noted, periodontal surgery may not be appropriate for uncontrolled DM patients. In this study, the effects of ERP in deep pocket sites on glycemic control were also determined. In Fig. 4C, the probing depth reduction was higher in the repeated SRP group than in the prophylaxis group. That is, in diabetes, ERP can increase the periodontal therapeutic effectiveness in patients with remaining deep periodontal pockets after the initial treatment.

To obtain more accurate results, the exclusion criteria and management of the study were strictly controlled. First, only T2DM patients were included; second, patients

with hopeless teeth or endodontic lesion that would lead to extraction or cause pain during the study, which would further affect the fluctuations in the plasma glucose concentration, were excluded; third, antibiotic administration was not used in this study. Given the generally stable HbA1c level in patients who did not receive other interventions, patients were assigned to the treatment group and the control group at a sample ratio of 2:1 to increase the sample size in the treatment group.

Another finding of the present study is that the different sensitivity of HbA1c to SRP may be caused by the different baseline glycemic condition. It was thought that the more severe the diabetes, the higher of the risk for therapy complications during periodontal therapy. In this study, no complication that can be correlated with periodontal therapy was found, although the highest HbA1c level reached 11.3%. Patients who showed decreased HbA1c levels 3 months after SRP treatment exhibited higher baseline FPG and HbA1c levels than those who exhibited unchanged or increased HbA1c levels. This result indicates that poorly controlled diabetes may be more sensitive to the short-term effect of SRP (within 3 months). Kardesler et al²⁷ reported higher HbA1c level reduction in poorly controlled T2DM patients (HbA1c $\geq 7\%$) than in well-controlled patients (HbA1c $< 7\%$) after a 3-month observation. However, 6 months later, no evident difference was found between the baseline FPG and HbA1c levels. Therefore, poorly controlled diabetes may react faster after SRP than well-controlled diabetes. In addition, the long-term effect may be similar. Given the small sample size in this study, additional work should be performed to confirm these results.

In conclusion, periodontitis patients with T2DM should receive SRP after a thorough examination, which improves the periodontal condition as well as glycemic control. ERP can further reduce the pocket depth in T2DM patients. Therefore, regular periodontal examination and SRP should be considered for diabetes-related healthcare, and ERP may be suitable for T2DM patients with deep periodontal pockets.

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References

- Mealey BL, Ocampo GL. Diabetes mellitus and periodontal disease. *Periodontol 2000* 2007;44:127–53.
- UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837–53.
- Mealey B. Diabetes and periodontal diseases. *J Periodontol* 2000;71:664–78.
- De Silva NT, Preshaw PM, Taylor JJ, Jayaratne SD, Heasman PA, Fernando DJ. Periodontitis: a complication of type 2 diabetes in Sri Lankans. *Diabetes Res Clin Pract* 2006;74:209–10.
- Albandar JM, Brunelle JA, Kingman A. Destructive periodontal disease in adults 30 years of age and older in the United States, 1988–1994. *J Periodontol* 1999;70:13–29.
- Van Dyke TE, Serhan CN. Resolution of inflammation: a new paradigm for the pathogenesis of periodontal diseases. *J Dental Res* 2003;82:82–90.
- Page RC. The pathobiology of periodontal diseases may affect systemic diseases: inversion of a paradigm. *Ann Periodontol* 1998;3:108–20.
- Rodrigues DC, Taba MJ, Novaes AB, Souza SL, Grisi MF. Effect of non-surgical periodontal therapy on glycemic control in patients with type 2 diabetes mellitus. *J Periodontol* 2003;74:1361–7.
- Navarro-Sanchez AB, Faria-Almeida R, Bascones-Martinez A. Effect of non-surgical periodontal therapy on clinical and immunological response and glycaemic control in type 2 diabetic patients with moderate periodontitis. *J Clin Periodontol* 2007;34:835–43.
- O'Connell PA, Taba M, Nomizo A, et al. Effects of periodontal therapy on glycemic control and inflammatory markers. *J Periodontol* 2008;79:774–83.
- Faria-Almeida R, Navarro A, Bascones A. Clinical and metabolic changes after conventional treatment of type 2 diabetic patients with chronic periodontitis. *J Periodontol* 2006;77:591–8.
- Yun F, Firkova EI, Jun-Qi L, Xun H. Effect of non-surgical periodontal therapy on patients with type 2 diabetes mellitus. *Folia Med (Plovdiv)* 2007;49:32–6.
- Grossi SG, Skrepicinski FB, DeCaro T, et al. Treatment of periodontal disease in diabetics reduces glycated hemoglobin. *J Periodontol* 1997;68:713–9.
- Stewart JE, Wager KA, Friedlander AH, Zadeh HH. The effect of periodontal treatment on glycemic control in patients with type 2 diabetes mellitus. *J Clin Periodontol* 2001;28:306–10.
- Jones JA, Miller DR, Wehler CJ, et al. Does periodontal care improve glycemic control? The Department of Veterans Affairs Dental Diabetes Study. *J Clin Periodontol* 2007;34:46–52.
- Christgau M, Palitzsch KD, Schmalz G, Kreiner U, Frenzel S. Healing response to non-surgical periodontal therapy in patients with diabetes mellitus: clinical, microbiological, and immunologic results. *J Clin Periodontol* 1998;25:112–24.
- Jenkins WM, Said SH, Radvar M, Kinane DF. Effect of subgingival scaling during supportive therapy. *J Clin Periodontol* 2000;27:590–6.
- Petersilka GJ, Ehmke B, Flemmig TF. Antimicrobial effects of mechanical debridement. *Periodontol 2000* 2002;28:56–71.
- Sigusch BW, Guntsch A, Pfitzner A, Glockmann E. Enhanced root planing and systemic metronidazole administration improve clinical and microbiological outcomes in a two-step treatment procedure. *J Periodontol* 2005;76:991–7.
- King Jr JT, Goulet JL, Perkal MF, Rosenthal RA. Glycemic control and infections in patients with diabetes undergoing noncardiac surgery. *Ann Surg* 2011;253:158–65.
- Silness J, Loe H. Periodontal Disease in Pregnancy. II Correlation between Oral Hygiene and Periodontal Condition. *Acta Odontol Scand* 1964;22:121–35.
- Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000;321:405–12.
- Simpson TC, Needleman I, Wild SH, Moles DR, Mills EJ. Treatment of periodontal disease for glycaemic control in people with diabetes. *Cochrane Database Syst Rev* 2010;5:CD004714.

24. Qin XY, Shen KT, Zhang X, Cheng ZH, Xu XR, Han ZG. Establishment of an artificial beta-cell line expressing insulin under the control of doxycycline. *World J Gastroenterol* 2002;8: 367–70.
25. Colwell JA. The feasibility of intensive insulin management in non-insulin-dependent diabetes mellitus. Implications of the Veterans Affairs Cooperative Study on Glycemic Control and Complications in NIDDM. *Ann Intern Med* 1996;124:131–5.
26. Hennessey JV, Bustamante MA, Teter ML, Markert RJ, McDonald SD. Bedtime dosing of glyburide and the treatment of type II diabetes mellitus. *Am J Med Sci* 1994;308: 234–8.
27. Kardesler L, Buduneli N, Cetinkalp S, Kinane DF. Adipokines and inflammatory mediators after initial periodontal treatment in patients with type 2 diabetes and chronic periodontitis. *J Periodontol* 2010;81:24–33.